Advanced Therapy in IBD: Mix and Match?

Vipul Jairath MBChB DPhil MRCP FRCPC

Professor of Medicine, Epidemiology and Biostatistics

Division of Gastroenterology,

Western University, London, Canada

Disclosures - Dr. Vipul Jairath

Type of Affiliation	Name of the Organization
Advisory Board / Consulting Fees	AbbVie, Alimentiv Inc (formerly Robarts Clinical Trials), Arena pharmaceuticals, Asahi Kasei Pharma, Asieris, Bristol Myers Squibb, Celltrion, Eli Lilly, Ferring, Fresenius Kabi, Galapagos, GlaxoSmithKline, Genentech, Gilead, Janssen, Merck, Mylan, Pandion, Pendopharm, Pfizer, Protagonist, Reistone Biopharma, Roche, Sandoz, Second Genome,Takeda, Teva, Topivert;
Speaker	Abbvie, Ferring, Galapagos, Janssen Pfizer Shire, Takeda

Disclaimer

- This is a talk “beyond the evidence” and describes off–label use
- Evidence for use of combination biologics in IBD is based upon successful case reports and case series
- We do not know enough about the safety and efficacy of this practice until the results of controlled trials which are underway, nor which combinations are optimal

Why Do We Need Combination Therapy in IBD?

What is the rationale for dual biologic therapy?

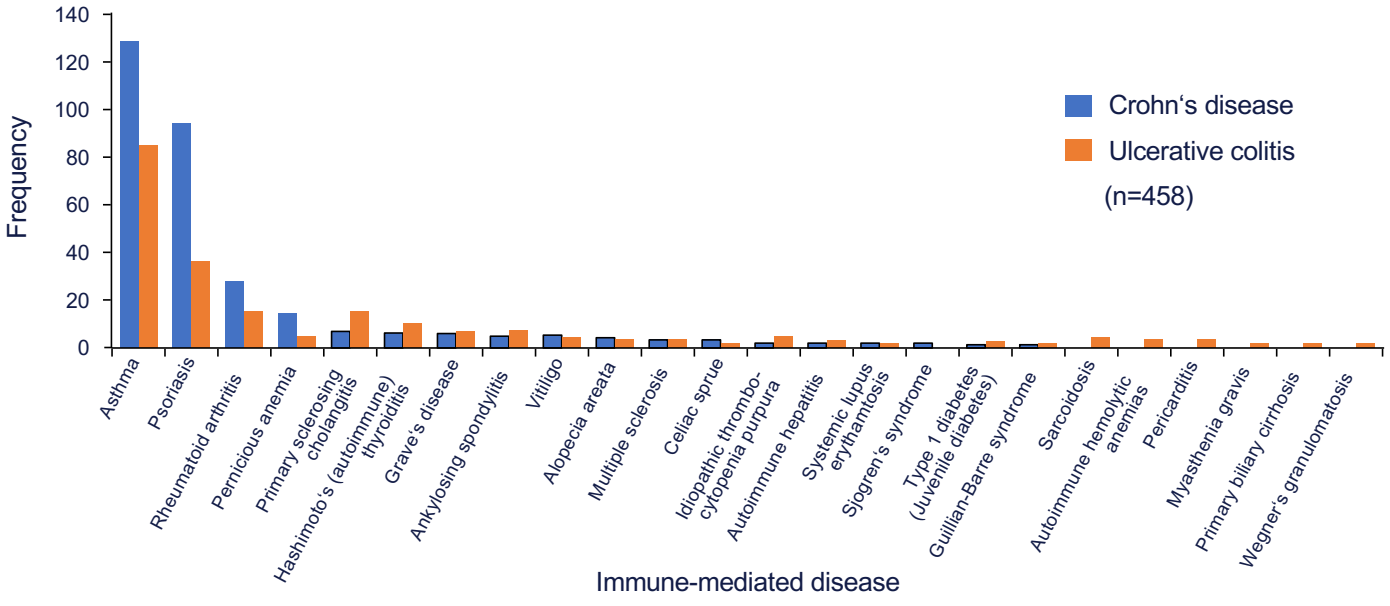
- Multiple pathways drive the immune-mediated inflammatory process
- Limited remission rates for biologics when used as single agents
- Mechanistic failure can develop over time for a single biologic agent
- Biologics used in succession tend to be less effective
- Agents effective for luminal disease may not be as effective for extraintestinal manifestations or other immune mediated disease

Theoretical Advantages of Combined Therapy

Advantages of Combined Therapy	Disadvantages of Combined Therapy
• Targeting multiple mechanism-greater efficacy • Prevention of immunogenicity • Increased drug concentrations	• Increased adverse effects & unknown safety risks • Complexity and cost of the regimen • Increased need for patient monitoring

IBD Burden Often Goes Beyond the Gut

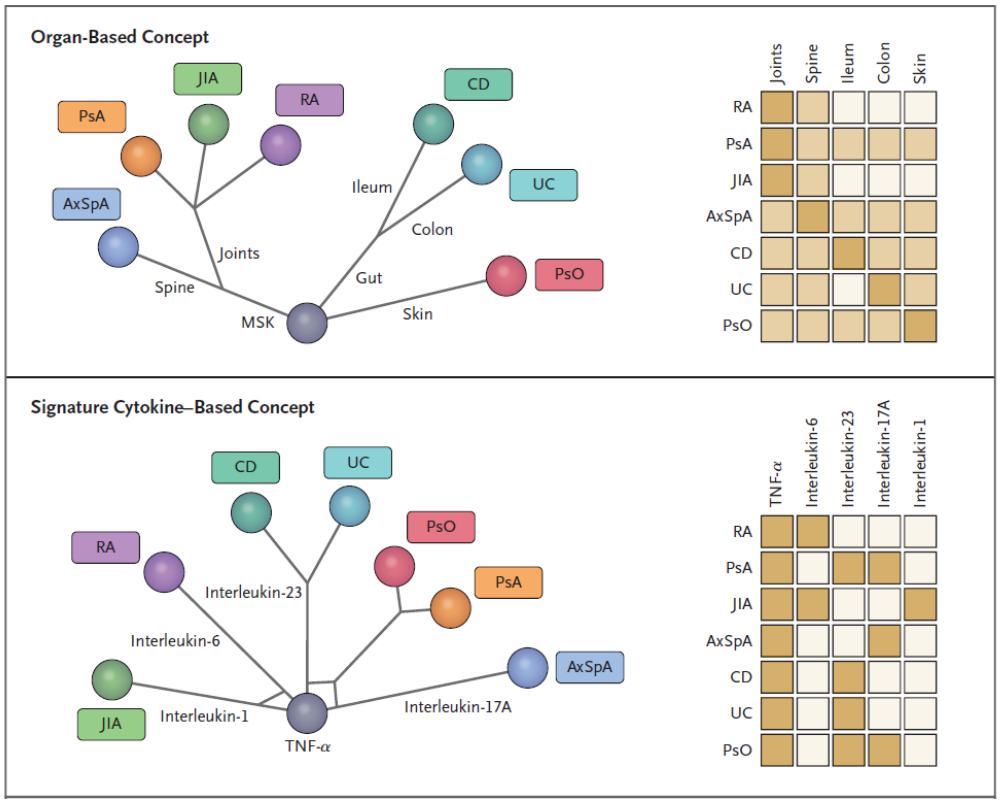
Prevalence of various immune-mediated diseases in patients with IBD, stratified by type of IBD[1]



IBD patients have been shown to be at 7.5 times higher risk of developing an immune mediated comorbidity than average non-IBD[2]

1. Conway G, et al. Aliment Pharmacol Ther 2017 Jan 20. doi: 10.1111/apt.13940

Choice of Mechanism Based on Co-existing Immune Conditions



Schett G, et al. N Engl J Med. 2021;385(7):628-639.

Choice of Mechanism Based on Co-existing Immune Conditions

Co-Existing Immune Condition	Primary Drug Consideration	Commentary
Plaque Psoriasis	Anti-TNF Ustekinumab MTX	Phase 2 trials suggested that apremilast was effective in UC
Psoriatic Arthritis	Anti-TNF Tofacitinib Ustekinumab MTX	Tofacitinib is in UC only and positioned after treatment with anti-TNF
Rheumatoid Arthritis	Anti-TNF Tofacitinib MTX	
Spondyloarthritis (AnkSpon and Sacroileitis)	Anti-TNF Tofacitinib	
Alopecia	Tofacitinib	
Multiple Sclerosis	Natalizumab Ozanimod	Natalizumab is only approved for CD Ozanimod is only approved for UC

Schett G, et al. N Engl J Med. 2021;385(7):628-639.

What situations can we consider Combination Strategies ?

- Refractory IBD

- Well controlled IBD but uncontrolled concomitant immune mediated inflammatory diseases (IMIDs)

Case 1: Refractory IBD

31 year old male, farmer

- Orchidectomy 2011 for testicular tumour
- Aggressive S/B CD 2011 with steroid dependency
- No response to MTx or Imuran
- Vedolizumab 2016-17: Partial response (Declined clinical trials)
- Ustekinumab 2017: Primary NR
- Infliximab 2017-19: Partial response
- Intra-abdominal abscess: R Hemicolectomy 2018
- Humira 2018, escalated to 80mg weekly
- Ischiorectal abscess 2021
- Scopes: Normal colon, strictured ileo-colic anastomosis
- MRE: Panenteric S/B CD with multiple strictures and long segments of inflammation (longest 60cm)

- Started Humira + Vedolizumab

Case 2: Controlled IBD, Uncontrolled IMID

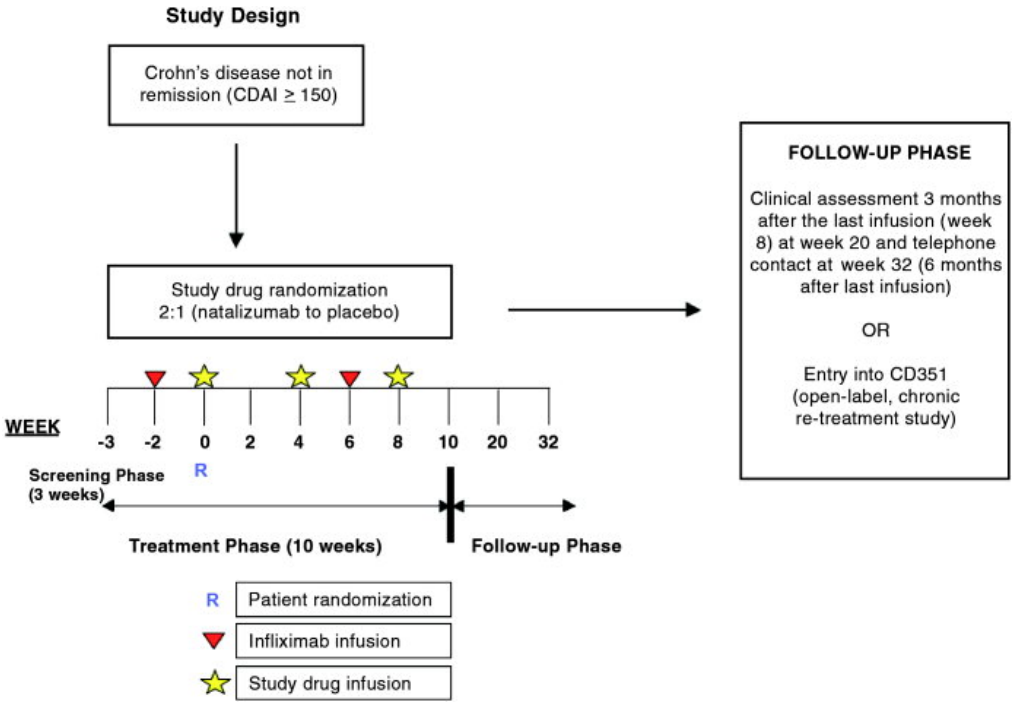
53 year old male

- Ileal and peri-anal CD ages 40 AND Ankylosing Spondylitis, with one IC resection and peri-anal disease
- Remicaide for 3 years helped CD and AS: secondary LOR
- Switched to Humira – partial response
- Switched to etanercept (primary NR)), switched back to Remiciade with severe infusion reaction
- Switched to Stelara (primary NR), then rheum added in secukinumab, which I stopped due to risk in CD
- Entered clinical trial of Rizankizumab but PNR
- Ileal disease responded to vedolizumab but AS worsened
- Switched to UPA 15mg/day by rheum- AS better

Started UPA+ Vedolizumab

Combination therapy is not a new concept

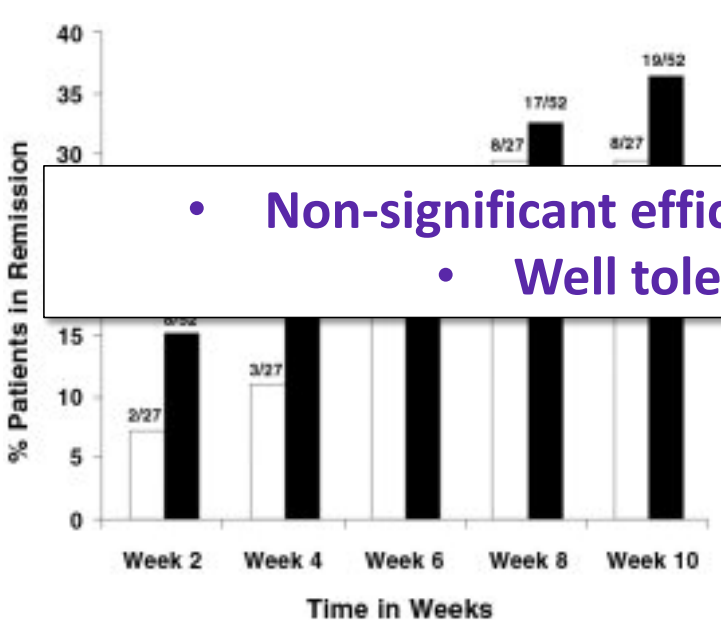
Infliximab + Natalizumab in Crohn's Disease



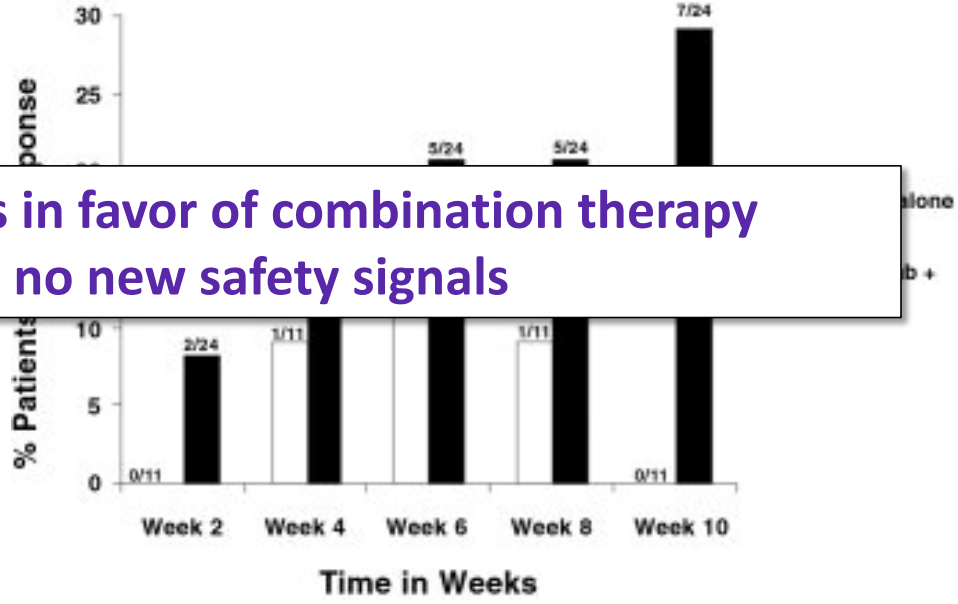
Sands B et al. Inflamm Bowel Dis 2007;13:2-11.

Infliximab and Natalizumab in Crohn's Disease

Clinical remission (CDAI < 150) over time.



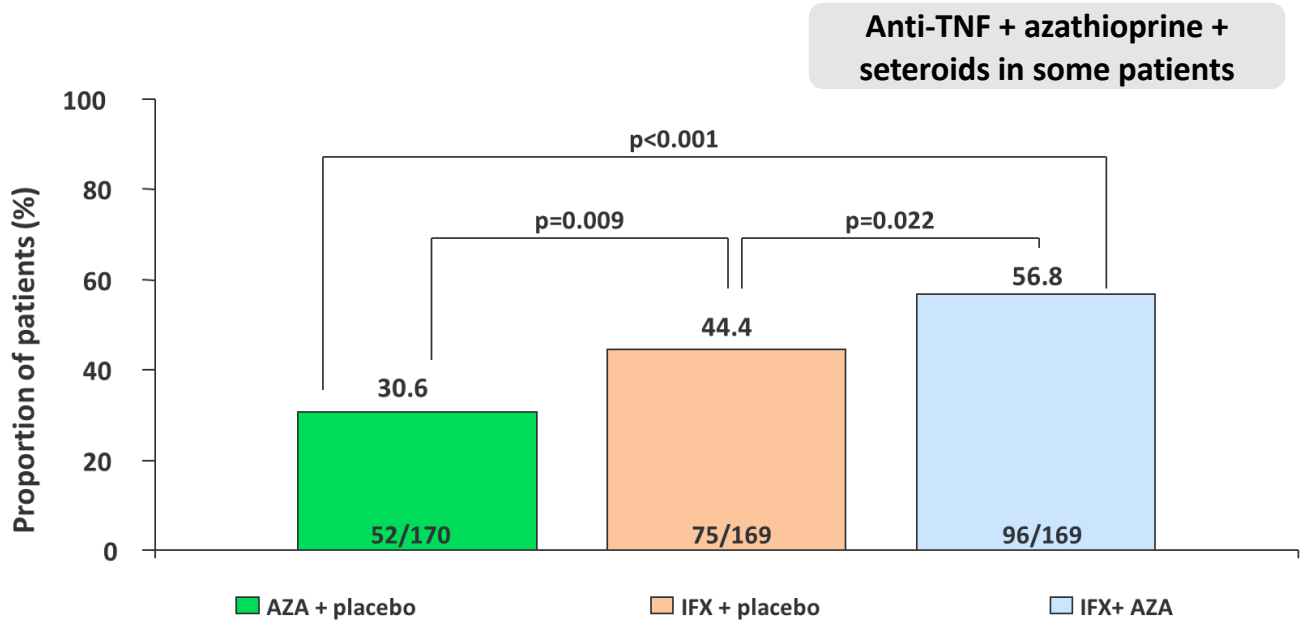
Clinical remission (CDAI < 150) in patients with baseline elevated CRP



- **Non-significant efficacy trends in favor of combination therapy**
- **Well tolerated with no new safety signals**

Sands B et al. Inflamm Bowel Dis 2007;13:2-11.

Combining IFX + thiopurine CD Patients: SONIC Steriod-Free Remission at Week 26



Colombel JF et al, N Engl J Med 2010

Understanding Combination Therapy IFX + AZA: Additive Effect vs. Enhanced Pharmacokinetics

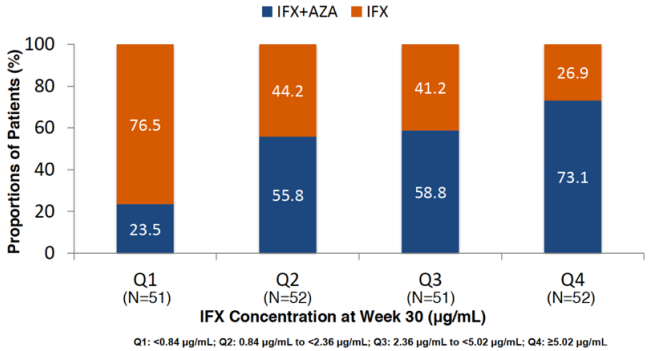
Methods

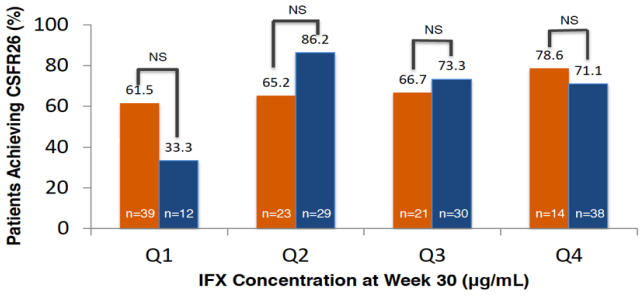
Exposure-response relationships within serum IFX concentration ranges were evaluated, with & without concomitant azathioprine (AZA), in 206 patients from SONIC.

Results

- No difference in steroid free clinical remission across quartiles.
- Non-significant benefit with addition of AZA in mucosal healing, only notable in 2 lower quartiles.

Benefit of combination therapy may be due to AZA's influence on PK of IFX, as well as additive effective and reducing immunogenicity



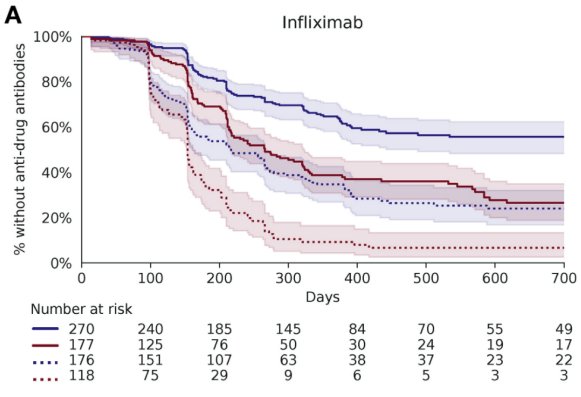


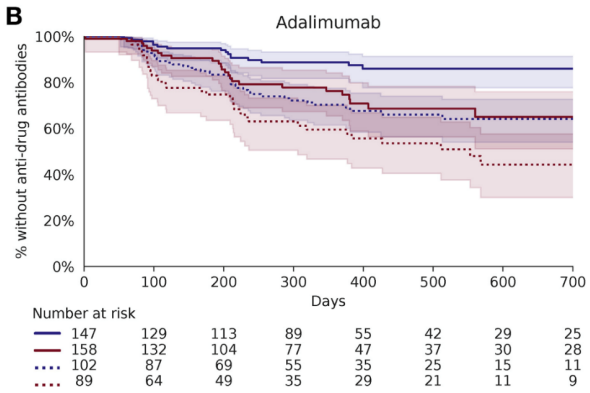
CSFR26 – corticosteroid free remission at week 26

Colombel JF et al, Clin Gastroenterol Hepatol. 2018 Sep 26. pii: S1542-3565

HLA-DQA1*05 Carriage Associated With Immunogenicity to Infliximab and Adalimumab

- **N = 1240**
- **Biologic-naïve CD patients starting infliximab or adalimumab**
- **Genome wide study**
- **HLA-DQA1*05 allele, significantly increased the rate of immunogenicity HR 1.90; 95%CI 1.60–2.25**



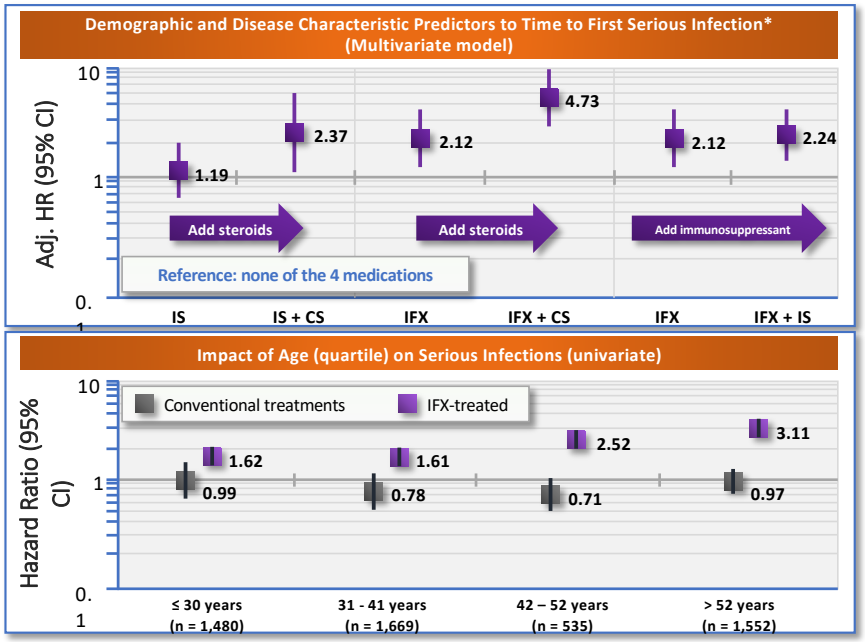


Dotted lines: anti-TNF monotherapy
Solid lines: combination therapy with immunomodulators
Red: carriers of the HLA-DQA1*05 allele(1 or 2 copies)
Blue: non-carriers

*Polling question on next slide

Sazonovs A, et al. Gastroenterology. 2020;158(1):189-199.

Risk of Infection with Combination Therapy



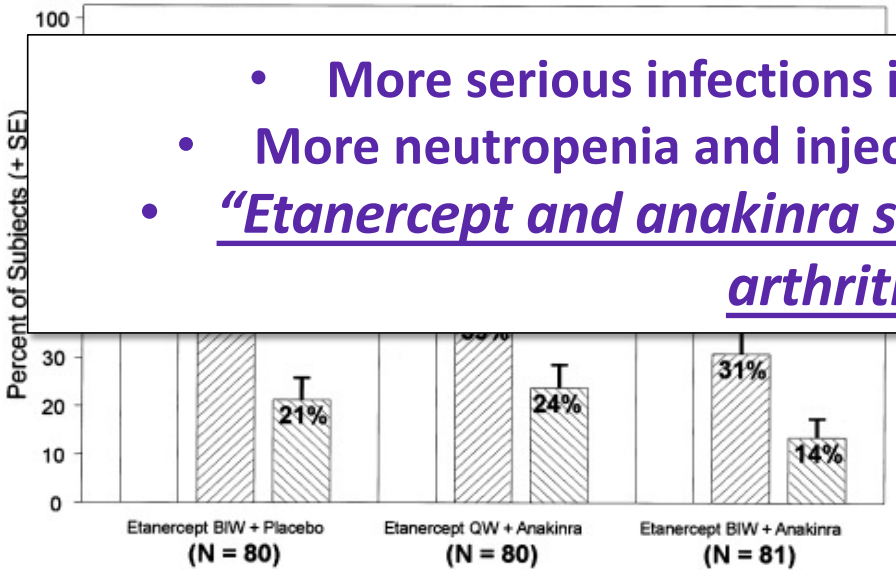
- TREAT registry revealed mild increase of serious infection in IBD patients treated with anti-TNF agents
  - Concomitant corticosteroid use resulted in a nearly five-fold risk of serious infection
- Univariate analysis identified increasing risk of infection with advancing age in Crohn's disease patients on infliximab therapy

Lichtenstein. GH 2011;7(8):suppl.13
Lichtenstein et al ECCO 2016 Abstract P368
Lichtenstein et al. DDW 2010. Poster Presentation

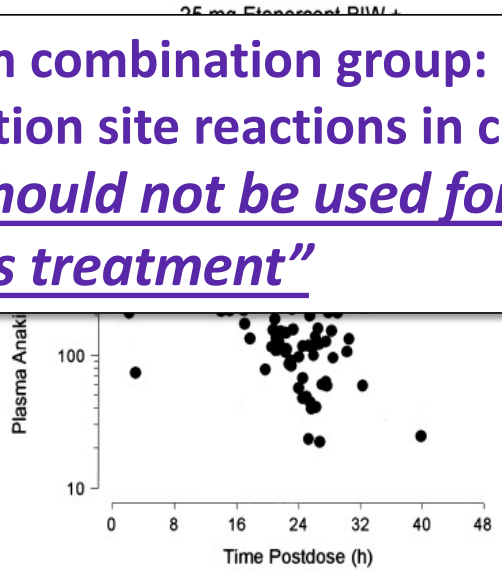
Combination therapy in Other Diseases

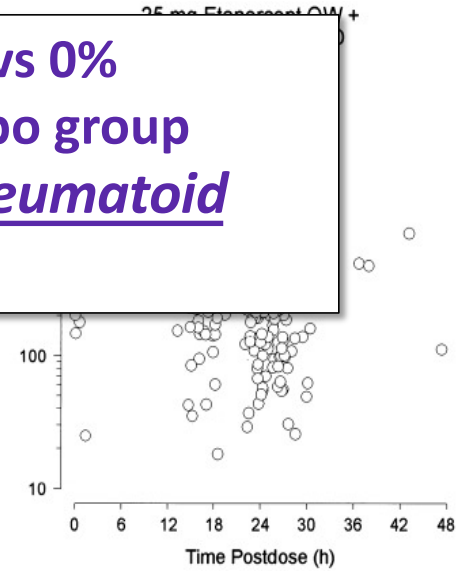
RCT: Etanercept + Anakinra in Rheumatoid Arthiritis

- 252 patients with Active RA despite MTx
- Combination therapy for 6 months provided no additional treatment benefit



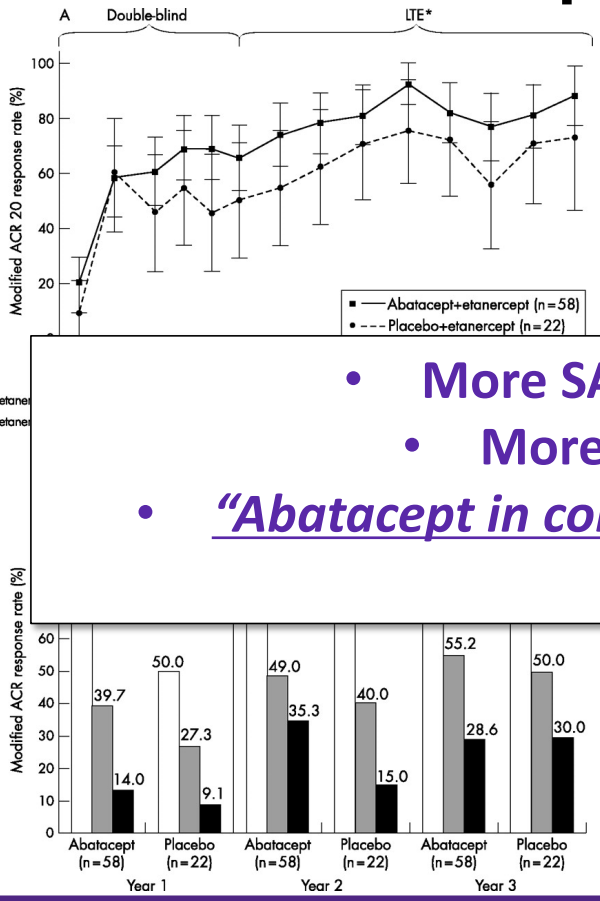
- **More serious infections in combination group: 7% vs 0%**
- **More neutropenia and injection site reactions in combo group**
- ***"Etanercept and anakinra should not be used for rheumatoid arthritis treatment"***





Arthritis & Rheumatism, Volume: 50, Issue: 5, Pages: 1412-1419, First published: 06 May 2004, DOI: (10.1002/art.20221)
Genovese M et al, Arthritis and Rheumatism, 2004

RCT: Etanercept + Abatacept in Rheumatoid Arthritis

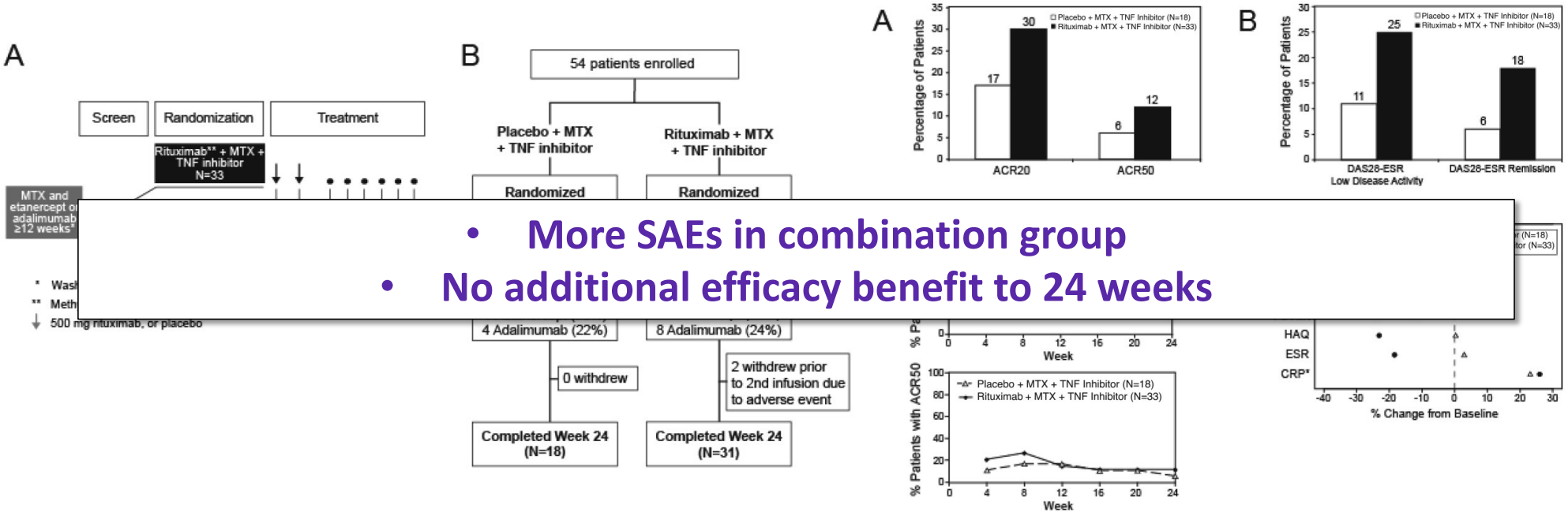


- 121 patients with Active RA on Etanercept, randomized to Abatacept or Placebo
- Combination therapy for 12 months provided no additional treatment benefit

- **More SAEs in combination group: 16.5% vs 2.8%**
- **More SIs in combination group: 3.5% vs 0%**
- ***"Abatacept in combination with etanercept should not be used for rheumatoid arthritis treatment"***

Weinblatt M et al., 2007 Feb;66(2):228-34

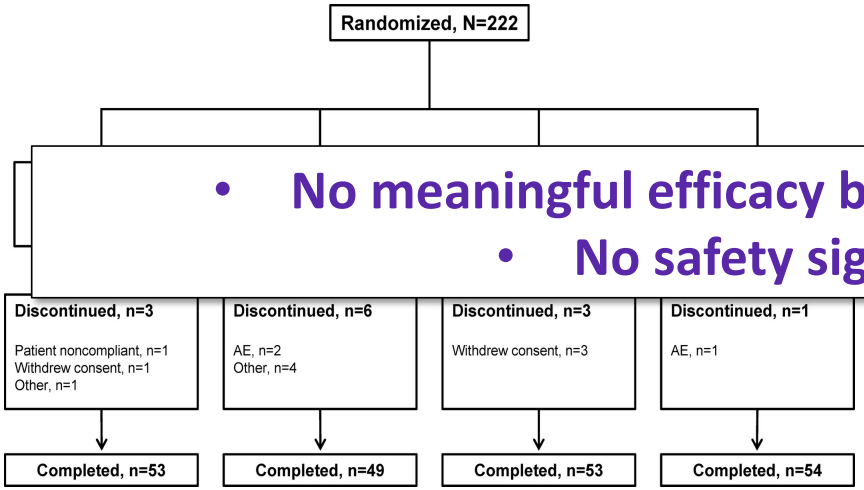
RCT: TNF/MTx + Rituximab in Rheumatoid Arthritis



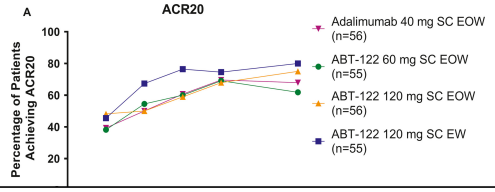
- More SAEs in combination group
- No additional efficacy benefit to 24 weeks

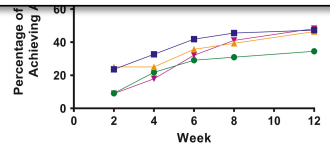
Greenwald M., 2011 Mar;63(3):622-32.
doi: 10.1002/art.30194

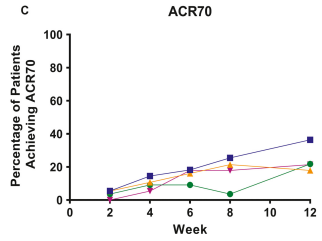
ABT-122, a Bispecific Variable Domain Immunoglobulin Targeting TNF and IL-17A, in Patients With Rheumatoid Arthritis With Inadequate Response to Methotrexate



- No meaningful efficacy benefit to 12 weeks over ADA alone
- No safety signals compared to ADA







Genovese M., 2018 Nov;70(11):1710-1720. doi: 10.1002/art.40580

Safety of Combination DMARDS in RA

- Meta-analysis of RCTs
- 623 subjects (410 combo; 213 single therapy)
- Median follow up 9.5 months (range 6-12 months)
- **0%)**
- **infections (6.7 vs 0.6%, OR 5.58, 95% CI 1.2-24.9, I^2 0%)** and the risk of SAEs remained significantly higher (17.1 vs 6.2%, OR 2.72, 95% CI 1.0-5.6, I^2 0%).

- **"Our findings suggest that combination therapy with two bDMARDs in RA appears to increase the risk of SAEs during the first twelve months of treatment"**

Case Series of Combination Therapy in IBD

Primary Literature on Dual Biologics in IBD

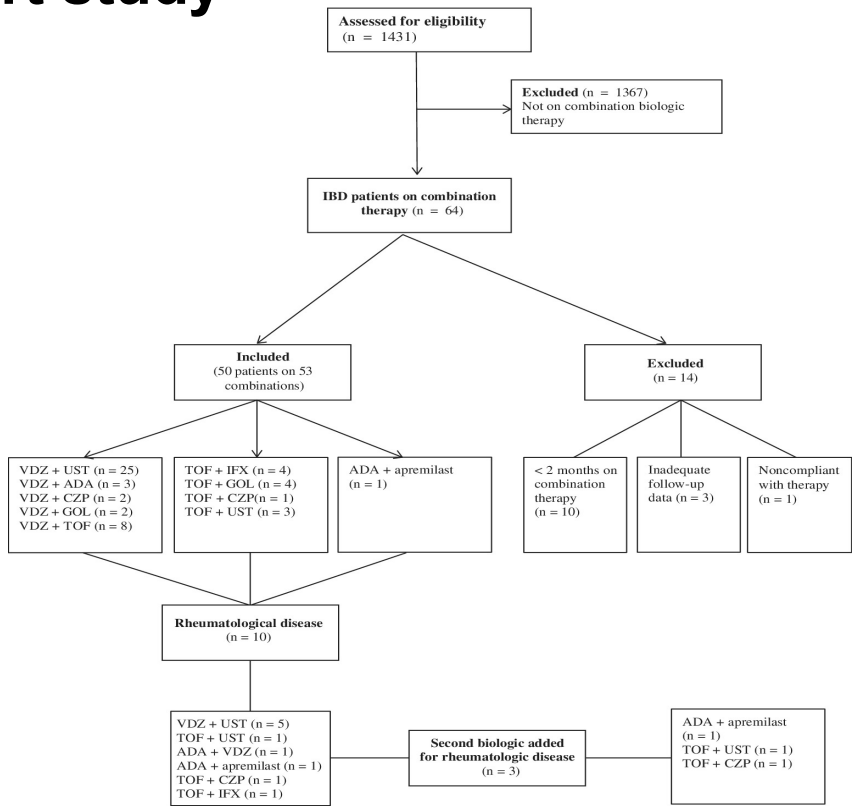
Study	Year	Study Type	Biologics	Number of Patients	Disease	Findings
Sands et al[3]	2007	RCT	IFX + natalizumab	79	CD	Combination therapy was well tolerated. Combination therapy was superior to IFX alone.
Glassner et al[6]	2020	Retrospective Cohort Study	Various	50	CD, UC	Increased risk of infection was seen in patients on combination therapy compared with biologic monotherapy; however, the risk was lower in those not on a concomitant immunomodulator.
Kwapisz et al[7]	2021	Retrospective Study	Various	15	CD, UC	Combination biologics with different mechanisms may be safe and effective; an anti-TNF or VDZ plus UST was most effective.
Privitera et al[5]	2020	Retrospective Study	Various	16	CD, UC	Three adverse events were reported; however, none of them were serious. Clinical response was seen in all patients.
Yang et al[4]	2020	Retrospective Study	Various	22	CD	Dual biologic therapy was associated with clinical, biomarker, and endoscopic healing in patients with refractory CD.
Olbjørn et el[11]	2020	CS	IFX + UST IFX + VDZ	13	CD, UC	This pediatric study demonstrated safety of combination therapy and clinical remission in 9 of the 13 patients
Buer et al[8]	2018	CS	Anti-TNF + VDZ	10	CD, UC	Dual biologic therapy in this study was safe and may represent a long-term treatment option for patients with refractory IBD.
Mao et al[27]	2018	CS	Various	4	CD	Dual biologic therapy with VDZ appears to be safe and effective.
Yzet et el[23]	2016	CS	Anti-TNF + UST	3	CD, UC	Use of dual biologic appears to be safe and well tolerated. Use of UST was not effective in the treatment of paradoxical psoriasis.

Combination biologic or small molecule therapy in IBD: Retrospective cohort study

Retrospective cohort study 2015-19
Houston Methodist, Texas

<u>Indication for DBT:</u>

- Partial Disease Response to 1st Biologic (labs/imaging/endo)
- IBD in remission, continued joint or skin Inflammation
- Joint or skin in remission, but on-going IBD activity



Glassner K et al. J Dig Dis 2020; 21(5) :264-271

Characteristics	IBD (N = 50)	CD (n = 31)	UC (n = 18)	IBD-U (n = 1)*
Age, y (mean ± SD)	36.7 ± 13.2	38.7 ± 13.9	34.1 ± 11.8	23
Male sex (n, %)	16 (32)	7 (23)	8 (44)	1 (100)
Ethnicity (n, %)				
Caucasian	38 (76)	23 (74)	14 (78)	1 (100)
Asian	2 (4)	0 (0)	2 (11)	0 (0)
Black	4 (8)	4 (13)	0 (0)	0 (0)
Hispanic	3 (6)	2 (6)	1 (6)	0 (0)
Arab	3 (6)	2 (6)	1 (6)	0 (0)
Disease duration, y (mean ± SD)	14.8 ± 11.1	17.8 ± 11.7	10.2 ± 8.1	4
Prior bowel resection (n, %)	20 (40)	20 (65)	0 (0)	0 (0)
Previous biologics, n (median [IQR])	2 (1–2)	2 (1.5–2.5)	2 (1–2)	1
Disease location				
Montreal classification (n, %)		L1: 2 (6)	E1: 1 (6)	L1: 0
		L2: 8 (26)	E2: 4 (22)	L2: 0
		L3: 21 (68)	E3: 13 (72)	L3: 1 (100)
		L4: 7 (23)		L4: 0
		P: 12 (39)		P: 0
Clinical disease activity at baseline (n, %)		HBI (n = 29)	Partial Mayo (n = 15)	HBI (n = 1)
		<5: 5 (17)	0-1: 3 (20)	<5: 0
		5-7: 9 (31)	2-4: 2 (13)	5-7: 1 (100)
		8-16: 11 (38)	5-6: 9 (60)	8-16: 0
		>16: 4 (14)	7-9: 1 (7)	>16: 0

Glassner K et al. J Dig Dis 2020; 21(5) :264-271

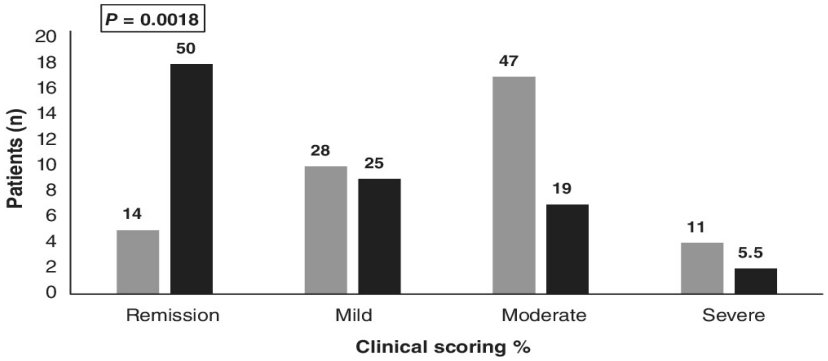
Combination biologic or small molecule therapy in IBD: Retrospective cohort study

Combinations	IBD (N = 53)	CD (n = 34)	UC (n = 18)	IBD-U (n = 1)
Vedolizumab + tofacitinib	8 (15.1)	0 (0)	8 (44.4)	0
Vedolizumab + ustekinumab	25 (47.2)	23 (67.6)	1 (5.6)	1 (100)
Vedolizumab + adalimumab	3 (5.7)	2 (5.9)	1 (5.6)	0 (0)
Vedolizumab + certolizumab	2 (3.8)	2 (5.9)	0 (0)	0 (0)
Vedolizumab + golimumab	2 (3.8)	1 (2.9)	1 (5.6)	0 (0)
Tofacitinib + infliximab	4 (7.5)	1 (2.9)	3 (16.7)	0 (0)
Tofacitinib + golimumab	4 (7.5)	0 (0)	4 (22.2)	0 (0)
Tofacitinib + certolizumab	1 (1.9)	1 (2.9)	0 (0)	0 (0)
Tofacitinib + ustekinumab	3 (5.7)	3 (8.8)	0 (0)	0 (0)
Adalimumab + apremilast	1 (1.9)	1 (2.9)	0 (0)	0 (0)

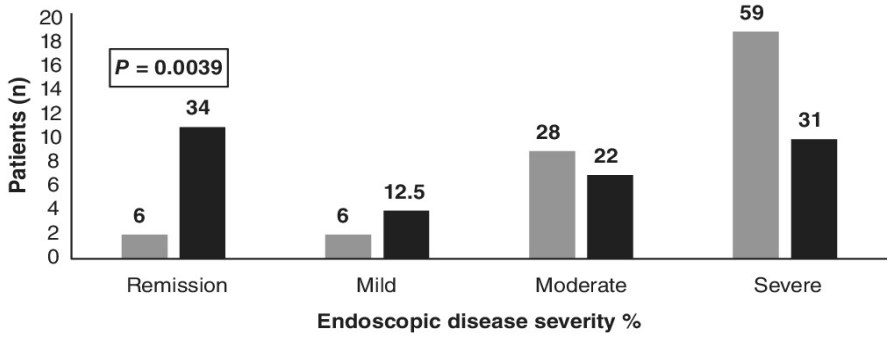
Glassner K et al. J Dig Dis 2020; 21(5) :264-271

Combination biologic or small molecule therapy in IBD: Retrospective cohort study

Clinical disease activity pre- and post-combination biologic therapy



Endoscopic disease activity pre- and post-combination biologic therapy



	Pre-therapy	Post-therapy	*P* value
ESR, mm/h (median [IQR])	17 (2-58)	13 (2-31)	0.002
CRP			002
Hem			022
Albu			017

Adverse events (n = 23)	Number of events
Enteric infection (n = 7)	3 bacterial enteric infections (*E. coli*), 3 *C. difficile* infection, 1 viral enteritis
Sinopulmonary (n = 7)	1 URI, 2 acute bronchitis, 3 sinusitis, 1 strep throat
Postoperative complication (n = 3)	1 peristomal cellulitis, 2 abdominal wall abscesses
Miscellaneous (n = 6)	1 viral warts, 1 UTI, 2 pelvic abscesses, 1 PICC line infection, 1 sepsis event secondary to PICC line infection + perianal abscess
Serious adverse events (n = 8)	1 bacterial enteric infection, 2 abdominal wall abscesses, 1 peristomal cellulitis, 2 pelvic abscesses, 1 PICC line infection, 1 sepsis event secondary to PICC line infection + perianal abscess

Glassner K et al. J Dig Dis 2020; 21(5) :264-271

Dual biologic therapy for CD – Two center experience

Retrospective cohort study

- 22 Crohn's disease patients from 2007-18
- Second biologic added (not combo induction)

Outcomes:

- > 50% reduction in SES-CD or endo assessment
- Clinical response / remission (PRO 2)
- Adverse events

24 trials of DBT amongst 22 patients

TABLE 1 Baseline characteristics

Characteristics	
Median age	35
Age at diagnosis < 16 y old	32% (7/22)
Female gender	55% (12/22)
Crohn's disease location	
Ileal	18% (4/22)
Colonic	27% (6/22)
Ileocolonic	55% (12/22)
Proximal involvement	5% (1/22)
Crohn's disease phenotype	
Inflammatory	5% (1/22)
Stricturing	59% (13/22)
Penetrating	36% (8/22)
Any history of perianal fistulas	55% (12/22)
Mean number of failed biologics	4
Immunomodulator	79% (19/24)
Steroid	33% (8/24)
Antibiotic	33% (8/24)
Prior surgery	91% (20/22)

Yang et al. APT. 2020;51:1031-38.

Dual biologic therapy for CD – Two center experience

TABLE 2 Description of prior biologic agents and dual biologic therapy (DBT) regimens: the median number of prior failed biologics was four

Reasons for prior biologic failure		Biologic at baseline prior to DBT initiation		Combinations of DBT	
Primary non-response	43% (40/96)	Vedolizumab	63% (15/24)	Vedolizumab/ustekinumab	33% (8/24)
Secondary non-response[a]	47% (44/96)	Ustekinumab	33% (8/24)	Vedolizumab/infliximab	25% (6/24)
Immunogenicity	7% (7/96)	Infliximab	4% (1/24)	Vedolizumab/adalimumab	17% (4/24)
Adverse event	3% (3/96)			Ustekinumab/adalimumab	8% (2/24)
				Vedolizumab/certolizumab	8% (2/24)
				Ustekinumab/infliximab	4% (1/24)
				Vedolizumab/golimumab	4% (1/24)

79% of DBT used biologic with secondary non-response prior
29% of DVT used biologic that has not previously been given

Yang et al. APT. 2020;51:1031-38.

Dual biologic therapy for CD– Two center experience

Primary outcome: endoscopic improvement during maintenance

- defined as either > 50% reduction in Simplified Endoscopic Score-Crohn's disease (SES-CD) or per endoscopist assessment

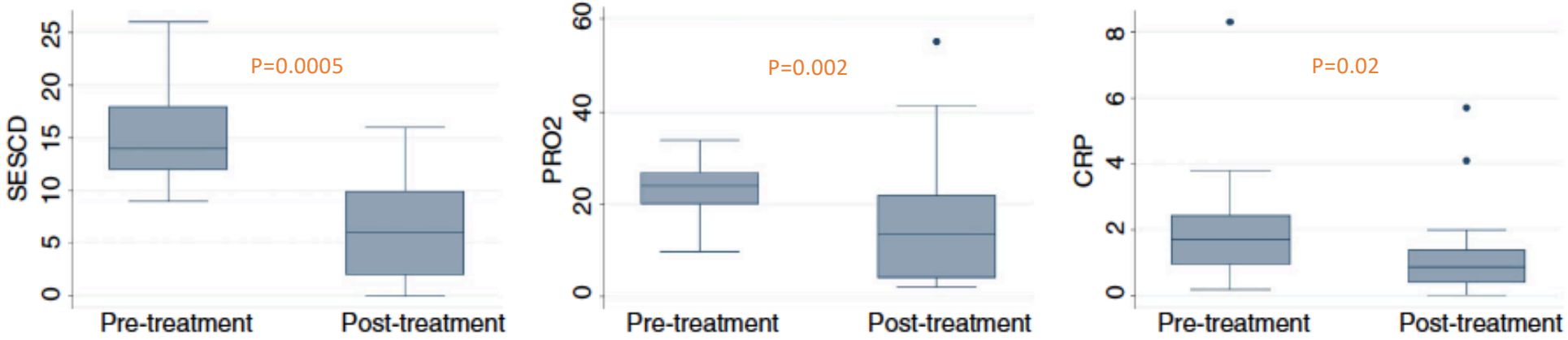


FIGURE 1 Endpoints of dual biologic therapy (DBT). A, SES-CD, simplified endoscopic score—Crohn's disease. B, PRO-2, Crohn's disease—patient reported outcome-2 score. C, CRP, C-reactive protein

Yang et al. APT. 2020;51:1031-38.

Dual biologic therapy – Two center experience

At 1 years 38% still on DBT

- Median treatment duration 274 days

<u>Surgery was needed in 33% cases</u>

Adverse events 13%

- Drug induced lupus with adalimumab
- Pneumonia
- Basal cell skin cancer
- Recurrent C diff

TABLE 3 Patient parameters and disease activity before and after treatment

	Baseline	Post treatment
PRO-2 score (median)[a]	24.1	13.4
Clinical remission	0/22 (0%)	9/22 (41%)
Mild	2/22 (9%)	2/22 (9%)
Moderate	20/22 (91%)	9/22 (41%)
Severe	0/22 (0%)	2/22 (9%)
Clinical response	n/a	11/22 (50%)
Endoscopic[b]		
Remission	0/23 (0%)	6/23 (26%)
Improvement	n/a	10/23 (43%)
C-reactive protein (median)	17 mg/L	9 mg/L
Albumin (median)	36 g/L	37 g/L
Perianal fistula present	12/24 (50%)	8/24 (33%)
Required surgery	n/a	8/24 (33%)
Adverse event	n/a	3/24 (13%)
Serious adverse event	n/a	2/24 (8%)

Yang et al. APT. 2020;51:1031-38.

ORIGINAL RESEARCH ARTICLE—CLINICAL

Safety of Combination Biologic and Antirejection Therapy Post–Liver Transplantation in Patients With Inflammatory Bowel Disease

Background: Patients with inflammatory bowel disease (IBD) post–liver transplant (LT) may have bowel inflammation requiring biologic therapy. We aimed to evaluate the safety of combination biologic and antirejection therapy in IBD patients after LT from a tertiary center case series and an updated literature review.

Methods: Inflammatory bowel disease patients undergoing LT between 1985 and 2018 and requiring combination biologic and antirejection therapy post-LT were identified from the London Health Sciences Transplant Registry (Ontario, Canada). Safety outcomes were extracted by medical chart review. For an updated literature review, EMBASE, Medline, and CENTRAL were searched to identify studies evaluating the safety of combination biologic and antirejection therapy in IBD patients.

Results: In the case series, 19 patients were identified. Most underwent LT for primary sclerosing cholangitis (PSC; 14/19, 74%) treated with anti-integrins (8/19, 42%) or tumor necrosis factor α (TNF) antagonists (6/19, 32%). Infections occurred in 11/19 (58%) patients, most commonly *Clostridium difficile* (4/19, 21%). Two patients required colectomy, and 1 patient required re-transplantation. In the literature review, 13 case series and 8 case reports reporting outcomes for 122 IBD patients treated with biologic and antirejection therapy post-LT were included. PSC was the indication for LT in 97/122 (80%) patients, and 91/122 (75%) patients were treated with TNF antagonists. Infections occurred in 32/122 (26%) patients, primarily *Clostridium difficile* (7/122, 6%).

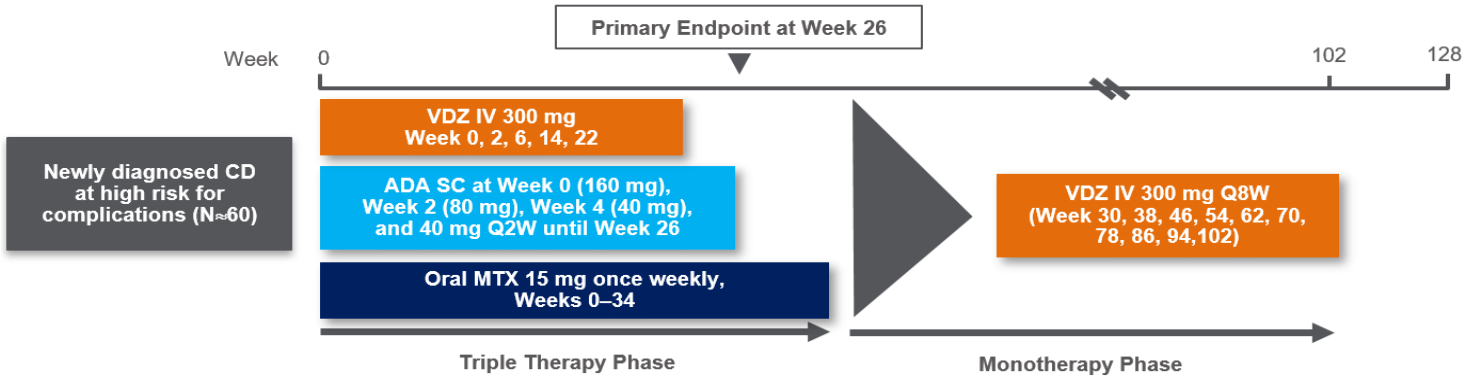
Conclusions: Inflammatory bowel disease patients receiving combination biologic and antirejection therapy post-LT appeared to be at increased risk of *Clostridium difficile*. Compared with the general liver transplant population in the published literature, there was no increased risk of serious infection.

Possible Combinations

	Anti-TNF	Selective anti-integrin	Anti-IL 12/23	Anti IL 23	Systemic JAK inhibitor	Local JAK inhibitor	S1P1 modulator
Anti-TNF	---	Yes	? Yes	?	No	Yes	? Yes
Selective anti-integrin	Yes	---	Yes	Yes	Yes	Yes	Yes
Anti IL 12/23	? Yes	Yes	---	---	? No	Yes	?
Anti IL 23	?	Yes	---	---	No	Yes	?
Systemic JAK inhibitor	No	Yes	No	No	---	No	? Yes
Local JAK inhibitor	Yes	Yes	Yes	Yes	Yes	---	Yes
S1P1 modulator	? Yes	Yes	Yes	Yes	No	Yes	---

Moving from Case Series to Clinical Trials in IBD

Combination of Biologics and Immunosuppressant EXPLORER



Objective

To determine the effect of triple combination therapy with an anti-integrin (VDZ IV), an anti-TNFα (ADA SC), and an immunomodulator (oral methotrexate) on endoscopic remission in participants with newly diagnosed CD stratified at higher risk for complications

Primary Endpoint

Endoscopic remission (SES-CD score from 0-2) at Week 26

Select Secondary Endpoints[a]

Endoscopic healing (SES-CD score ≤4 + reduction from baseline SES-CD score of ≥2 points + no individual SES-CD subscore >1)

Endoscopic response (At least 50% reduction of baseline SES-CD score)

Deep remission (CDAI<150 + SES-CD score from 0–2)

[a]Evaluated at Weeks 26, and 102

ADA=adalimumab, CD=Crohn's disease; CDAI=Crohn's Disease Activity Index, MTX=methotrexate; Q2W=every 2 weeks; Q8W=every 8 weeks; SES-CD=simple endoscopic score for Crohn's disease; VDZ=vedolizumab

VEGA: Guselkumab + Golimumab

STUDY

- Phase 2a, randomized, double-blind, placebo-controlled, active-comparator-controlled, parallel-group, proof-of-concept, multicentre study

PURPOSE

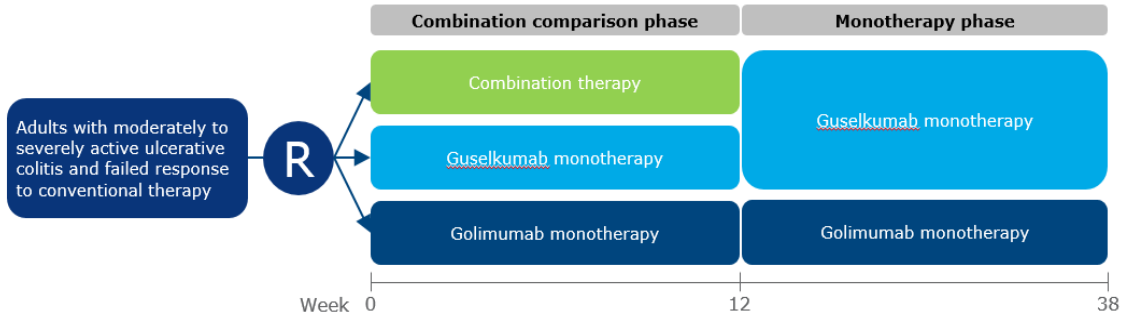
- To evaluate the safety and efficacy of combination therapy with guselkumab and golimumab in patients with moderately to severely active ulcerative colitis

PRIMARY ENDPOINT

- Clinical response at Week 12 defined by Mayo score

MAJOR SECONDARY ENDPOINTS

- Clinical remission at Week 12 defined by Mayo score



Duet UC and Duet CD

DUET – CD Crohn's Disease

Study Description	First in class, combination study evaluating efficacy and safety of Guselkumab and Golimumab. Active control only
Phase	**IIb**
Drug	**Guselkumab / Golimumab Combo**
Route	Intravenous
Target	IL-23 / TNFa
Treatment Period	48 weeks
Active Comparator	**Guselkumab and Golimumab Monotherapy**
Placebo	None
LTE (duration)	4 Years
Population	**Mod-Sev CD**
Bio-naïve	None
Bio IR (min %)	100%
Prohibited med hist	Intolerance to Guselkumab and/or Golimumab
Endpoints	Clinical remission and endoscopic remission

DUET – UC Ulcerative Colitis

Study Description	First in class, combination study, evaluating efficacy and safety of Guselkumab and Golimumab. Active control only
Phase	**IIb**
Drug	**Guselkumab / Golimumab Combo**
Route	Intravenous
Target	IL-23 / TNFcx
Treatment Period	48 weeks
Active Comparator	**Guselkumab and Golimumab Monotherapy**
Placebo	None
LTE (duration)	4 Years
Population	**Mod-Sev UC**
Bio-naïve	None
Bio IR (min %)	100%
Prohibited med hist	Intolerance to Guselkumab and/or Golimumab. IL-23
Endpoints	Clinical remission and endoscopic remission

Considering Dual Biologics for Refractory IBD?

- Review medical records in detail to understand whether reported prior biological failures were indeed true failures (and the nature of these)
- Try combination with a different immunomodulator
- Engage with the nearest clinical trial center to assess eligibility for a trial
- Ensure the patient has seen a colorectal surgeon and surgery truly not an option
- Failing these options:
  - Combination biologic/small molecule could be carefully considered with clear counselling regarding their off-label use and unknown safety concerns.
  - Weigh against risk of untreated disease (recurrent surgery, TPN etc)
  - A defined period of time (e.g. 6 months) should be agreed upon with re-assessment
  - Vedolizumab or Ustekinumab most appropriate anchor biologic